An Assessment of the Massachusetts Biotechnology Industry

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A project of

The Massachusetts Centers of Excellence Corporation

Bay State Skills Corporation

Massachusetts Biotechnology Council, Inc.

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INTRODUCTION

The following assessment of the status of biotechnology in Massachusetts was designed to provide an informed overview of this fledgling industry. It represents the first attempt to document the status of biotechnology in the Commonwealth. Though the authors and the supporters of this project are admittedly biotechnology advocates, we have sought to temper our sponsorship by avoiding overtly promotional positions.

The goal of this project is to provide an insider's view of biotechnology by documenting concepts generally held as common knowledge or by revealing false assumptions. We therefore included extensive background information to place the data in a broader context and to enable a clearer understanding of the biotechnology culture.

Though it is impossible to produce definitive numbers for an evolving industry, we have attempted to use the data to make appropriate informed projections. We realize that this information will not eliminate controversy, but may provide an informed, common baseline for future discussions.

The report is based on data collected in the spring of 1990. A majority of the biotechnology companies in Massachusetts participated in a written survey, and the authors drew materials from responses to this survey as well as from publicly available documents and telephone interviews.

Our effort was generously supported by the Massachusetts Centers of Excellence Corporation, the Bay State Skills Corporation and the Massachusetts Biotechnology Council.

OVERVIEW

It is now more than 12 years since the first dedicated biotechnology companies were founded in Massachusetts. Today, Massachusetts is one of the world centers of the industry. Exactly how much biotechnology will contribute to the local economy and how it will eventually affect the way we live is open to debate, but few who possess any knowledge of the industry dispute Massachusetts' current position as one of its leaders.

The leadership of Massachusetts in biotechnology raises two critical questions: How long will the state be able to retain its primary position as the industry matures? Will Massachusetts' pre-eminence in research be converted into long-term commercial leadership, or will the Commonwealth provide the brain trust for application of the technology elsewhere? The answers will be determined by a number of forces out of our control, such as broad economic trends and the nature of future scientific discoveries, but both the commitment of the state's leaders to cultivate and attract biotechnology and the sensitivity of the industry to the needs of the Commonwealth will indeed be critical factors.

Biotechnology as defined in this study is the commercialization of modern biology. We purposefully sought a definition that would be inclusive and generous because the applications of the new biology continue to broaden, and the "biological revolution" that is driving the commerce has taken many unexpected turns.

We included only for-profit organizations in the poll and did not include companies providing services to the industry. We excluded from the sample those companies that make medical devices, products such as catheters and pacemakers. (However, there is indeed a large and growing medical device industry in this state that shares many of the roots,

needs and concerns of biotechnology.) We included diagnostic companies, companies making human therapeutics, agricultural companies and the manufacturers of apparatus or supplies intended for use primarily by biotechnology companies. Companies which met the above parameters but did not view themselves as members of the biotechnology community were not included in the results.

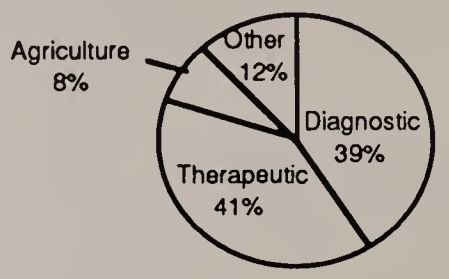
This process produced a list of 116 companies in Massachusetts fulfilling the broad definition of biotechnology.

Biotechnology emerged in Massachusetts because of the concentration and strength of its research centers. Just over 84 percent of the companies responding to the survey said that proximity to a university was important and 35 percent listed it as their first priority in site selection. For this reason, Cambridge alone is home to 33 biotechnology companies. In addition, biotechnology companies tend to locate in towns with regulatory codes in place rather than hazard an unproven regulatory environment.

Currently, approximately 13,600 individuals are employed at biotechnology companies in Massachusetts. On average, the participating companies expect an approximate increase in staffing of 57 percent by 1993 and an increase of about 488 percent by the end of the decade. However, these numbers reflect the employment projections for the companies and not how many of their employees will be located in Massachusetts, nor does the response account for either business failures or new companies or for subsidiaries of large pharmaceutical companies locating here.

Massachusetts Biotechnology Profile

Number of Companies	116



Total Number of Employees	13,606
Total Annual Expenses in MA	$1,328M
Total Annual Payroll	$432M
Total Cash Reserves	$1,404M

Projected Increases in Staffing	In 3 Years	In 10 Years
Research and Development	44%	194%
Administration	35%	284%
Manufacturing	93%	686%

Anticipated New Product Introductions by 1993	
Diagnostic	164
Therapeutic	36
Agricultural	20

The biotechnology industry should continue to experience significant growth through the 1990's as the first major products of the industry reach the market. One consistent message resulting from the survey, however, was that although Massachusetts' pre-eminence in R&D has given it a lead in the biotechnology industry, there can be no guarantee that the continued growth of these companies will occur here. Manufacturing, which holds the greatest promise for employment and local expenditures, does not have to be located close to senior management or R&D. Alternatively, there is no reason to conclude that manufacturing will not locate in the Commonwealth, only that there will be intense competition for these sites.

The private sector, particularly the local real estate industry, has been making a significant commitment to the recruitment of biotechnology companies to Massachusetts, but the public sector has been far

less active in seeking new biotechnology companies than have other states. It is also clear that the Massachusetts research community has the potential of attracting the R&D arms of major pharmaceutical companies to the state as well as start-ups.

Because 67 percent of the companies surveyed are not showing a profit at this time, financial worries lead the industry list of near-term concerns. Although biotechnology is not a labor-intensive business, it can make a significant economic contribution through induced economic impact as dollars generated by biotechnology companies cycle through the the local economy. The availability of private financing will be critical to the continued growth of the biotechnology industry. If consolidation becomes the only means of fueling growth, the total number of companies may shrink and the founding of new companies may slow.

BACKGROUND

In the 1970's, the world was dazzled by advances in molecular biology. "Gene splicing" conjured science fiction visions, and the technology was touted as both a cure for all human ills and a threat to civilization. Few understood the technology, and fewer still had a true understanding of its potential, but it was clear that the public was getting its first glimpse of a technological revolution.

The biological revolution began in 1952 with the discovery of the structure of DNA by James Watson and Francis Crick. By visualizing the structure of the DNA molecule, scientists gained insight into how it instructed cells to perform specific tasks and how that information was transferred from cell to cell. However, it was not until 1976 with the founding of Genentech in San Francisco that the technology had advanced far enough to be commercialized. Since the founding of Biogen in 1978 and Genetics Institute in 1980, the Massachusetts biotechnology industry has grown to well over 100 biotechnology companies. There are currently approximately 1100 biotechnology companies in the United States as estimated in a recent survey by Ernst & Young.

Initially, gene splicing was the miracle that drew public attention. By manipulating the genetic code, scientists were able to alter the basic instructions of life; in essence, to create what appeared to be new living beings. However, the true breakthrough of biotechnology was its ability to make large, complex molecules called proteins, the basic chemical building block of life. Human DNA, it was discovered, could be inserted into primitive microorganisms and instruct them to produce large amounts of relatively pure human proteins. Because proteins are made by organisms with "recombined" DNA, they are called recombinant proteins. Traditional chemical processes cannot make these molecules because they are too complex and too

large. It is the understanding and manipulation of proteins, as pharmaceuticals, diagnostics and industrial or agricultural products, that is currently the primary business of biotechnology.

The medical uses of biotechnology have developed from the understanding that many diseases are caused by protein imbalances. Some diseases can be fought by correcting these imbalances or by bolstering the immune system with large quantities of recombinant proteins made by genetically engineered microorganisms. For example, the proteins involved in the natural healing of the human body or its disease-fighting mechanism can be made in large enough quantities to be used to treat disease. Such treatments can either replace proteins that the human body is unable to produce on its own (such as Factor VIII, the absence of which results in hemophilia) or provide proteins that buttress the body's battle against disease (such as alpha interferon, useful in fighting cancers and infections). In the past, the only proteins available for treating disease, such as insulin or human growth hormone, were obtained by processing animal or cadaver tissue.

Since all life begins as a single cell, genetic engineering can also be used to alter the genetic characteristics of complex animals and plants. For example, it is possible to develop animals that grow quickly or larger on less feed, or plants that are disease resistant or higher in desired nutrients.

Presently, human therapeutics based on recombinant proteins are the products most often associated with biotechnology. However, a large number of diagnostic companies have been formed to develop and manufacture products to detect infections and diseases such as hepatitis and AIDS. Diagnostics are simpler to develop than pharmaceuticals but generally have a shorter product lifetime. Companies devoted to agricultural products were formed early (BioTechnica was founded in 1981), but grew more slowly primarily due to the inherent difficulties of working with plants, such as slow reproductive cycles. (It takes months to grow a plant to maturity so that seeds can be collected whereas bacteria duplicate in minutes.) Finally, companies were established that supply equipment for use by genetic engineering companies, such as

Millipore's MilliGen division, which makes gene splicing machines for isolating and analyzing DNA, and New England BioLabs, which makes enzymes and reagents for laboratory and industrial use.

In many ways the growth of biotechnology parallels the commercial application of chemistry and physics which began fifty years ago. Basic discoveries in these sciences produced synthetic fibers, petrochemicals and miniaturized computers. Over the last decade, biotechnology has similarly broadened its scope as scientists find new ways of applying the basic science to broad applications. If one were to compare the commercialization of modern biology with the commercialization of physics to produce computers, biotechnology is still in the large mainframe phase of its development: its applications are only those capable of bearing its costs; it is still closely linked to academic research; and traditional industries have not yet adopted the still emerging technology.

Research is still in its early stage, but scientists are developing means of implanting genetic information directly into humans and animals. By using these "gene therapy" techniques, physicians will be able to instruct a patient's own cells to produce the proteins needed to combat disease and to support health. Such therapies represent a future generation of biotechnology products.

Although early in its development biotechnology could clearly also be used to improve a variety of industrial processes and agricultural applications, biopharmaceuticals were developed first because their social and economic value was sufficient to absorb the costs of the new technology. In the near future, however, food products enhanced through genetic engineering should begin to appear, and eventually many of the consumer and industrial products manufactured from natural materials will also be affected by biotechnology.

When considering this potential diversity, it becomes clear that biotechnology is not an industry, but a means of production. Just as Henry Ford established the automotive industry not by inventing the motorcar, but by developing an efficient means of making it, biotechnology will create new products by enhancing their discovery and manufacture.

Understanding this concept is key to understanding the impact of biotechnology. What biotechnology can do is allow us to discover biological compounds we could not find before, improve products that we were unable to make efficiently, and gain valuable qualities that enhance current products.

Eight years ago biotechnology produced its first usable products. These recombinant drugs (such as alpha interferon, tissue plasminogen activator, human growth hormone, human insulin and erythropoietin) are now saving lives and producing hundreds of millions of dollars in revenues. A long list of such "biopharmaceuticals" is about to reach the market: Factor VIII, blood growth factors, gamma interferon, glucocerebrosidase, monoclonal antibodies to fight cancers and new vaccines. All are made by Massachusetts-based companies.

Why Massachusetts?

Early biotechnology companies were attracted to Massachusetts by the pre-eminence of its research institutions. Eighteen Nobel laureates are actively working in the biological sciences at Harvard and MIT. Both of these universities made major commitments to molecular biology in the 1950's. MIT hired Salvador Luria to build its program and Harvard established a laboratory around James Watson. Both universities subsequently hired leading researchers such as Walter Gilbert, Mark Ptashne, Jeremy Knowles, Phillip Sharp, Daniel I.C. Wang, Robert Weinberg and many others which proved critical in the attraction of venture capital to Massachusetts to fund new companies. Both of these research institutions now have an active, professional licensing office providing a continuing flow of new discoveries for commercial development.

In addition to the university research centers, the extensive Boston medical community with its complex of teaching hospitals makes significant contributions to biomedical research. One of these in particular, The Massachusetts General Hospital, has established itself as the leading medical research center working in the field of biotechnology. The MGH currently has research agreements with several major health care firms, including Hoechst for $68 million, Shiseido for $85 million and Bristol-Myers/Squibb for $37 million. Another teaching hospital, The Dana-Farber Cancer Institute, provided

the early research for ImmunoGen, Inc., a biotechnology company developing cancer fighting monoclonal antibodies.

Finally, the Massachusetts business community -- lawyers, accountants, bankers, architects, and others -- is intimately familiar with the needs of the biotechnology industry. Locating a biotechnology company in the Commonwealth means instant access to these important resources.

This infrastructure of universities, medical research centers, corporations and support services has created an environment conducive to the commercialization of modern biology unsurpassed anywhere else in the world.

The Lengthy Product Development Cycle

New commercial applications of biology continue to appear as successive waves of companies are founded in response to laboratory breakthroughs. Each new generation broadens the definition of biotechnology and moves its commercial application further from the simple manufacture of human proteins through genetic engineering.

As indicated by the survey, the founding of these companies tends to be cyclical, reoccurring every two or three years, while the product development cycle is far longer, ranging from three to eight years. Though several generations of biotechnology companies have been founded, only the oldest companies are now bringing products to market.

The extraordinary product development times are caused both by the time involved in the exploration of new scientific territory and by the legally prescribed regulatory review process. It takes from three to four years to develop and test a diagnostic product; six to eight years to develop and test a pharmaceutical product, and yet longer to develop products for agricultural use. Each new drug must be proven safe and effective to the satisfaction of the United States Food and Drug Administration before it can be generally used by doctors to treat disease. Agricultural products must pass similar approval hurdles at the Department of Food and Agriculture and the Environmental Protection Agency.

Since the biotechnology product development cycle is far longer than the general business cycle and longer still than the public's attention span, a company will pass through periods of both intense investor interest and intense skepticism between its founding and its first product.

Not only is this a lengthy process, but it is also extremely expensive. According to the Pharmaceutical Manufacturers Association, the average cost of developing and testing a new pharmaceutical product is $125 million. Although biotechnology companies have been able to reduce both the cost and time involved in pharmaceutical development, they still require multiple rounds of financing and extensive support from larger companies before product sales become an important source of revenue.

Prior to product sales, the value of a biotechnology company is established primarily by the credibility of its business plan over time as determined by achieving announced goals. Theoretically, if a company achieves timely scientific advances it will gain the public's attention and be able to raise capital when needed rather than when available. In reality, few companies have the luxury of remaining silent while completing their research. Most are compelled by the continuing need to raise capital to actively draw attention to corporate events through public relations activity.

Currently, the older companies dominate the public perception of biotechnology as their first products reach the market. Genetics Institute, for example, was founded in 1980 and currently has 530 employees, cash reserves of over $100 million and seven products in clinical trials. It is planning to launch a number of pharmaceutical products based on recombinant proteins in the next few years, and, in terms of staffing, is the largest biotechnology company in Massachusetts.

The public perception of success of the products of companies such as Genetics Institute will significantly affect the ability of smaller companies to attract the interest of potential investors and corporate backers. For example, Cambridge NeuroScience, Inc., which began operations in 1986

and is recognized as a leader in the development of treatments for Alzheimer's disease, schizophrenia and other central nervous system diseases, is far less well known by the public. It is one of many recently founded neuroscience companies, several of which are located in the Boston area. Cambridge Neuroscience currently has about $5 million in cash reserves, 55 employees and no product candidates in human trials. Its product candidates are based on a new understanding of central nervous system chemistry and the application of genetic engineering as a research tool for the development of new drugs. For Cambridge Neuroscience to grow to a mature company it will require strong corporate partners and significant financing, all based on the confidence of investors that the underlying technology is valid and the probability of successful product development is high.

Much of Massachusetts' leadership in biotechnology is due to the abundance of small companies such as Cambridge Neuroscience on the cutting edge of the technology. These companies locate here because they want to be close to the scientists who generate new ideas and solutions to development problems. Unlike traditional businesses that are market driven, the biotechnology cycle is driven by the availability of financing and new technologies that capture investor interest. Therefore, the growth of biotechnology is not as smooth as one would expect of an industry expanding to meet market demand. Since both the press and the public are accustomed to this more traditional linear market-driven growth, the down cycles are often accompanied by proclamations of doom by industry observers equal to the exhilaration expressed at successive growth periods.

Regulations

Biotechnology companies face several levels of regulations. Of primary importance are the federal regulatory agencies, which must approve all pharmaceutical and agricultural products prior to marketing. Locally, a wide variety of regulations cover everything from recombinant research to plumbing codes. Most of the local regulations are controlled by cities and towns.

The Food and Drug Administration, the Department of Food and Agriculture and the Environmental Protection Agency are the critical national

biotechnology regulatory bodies. They are the final arbiters determining which products, after the investment of tens of millions of dollars, actually reach their intended markets.

A human therapeutic product based on a biopharmaceutical normally takes from six to eight years to pass through the approval process, tested first in animals and humans. Regulatory bodies have generally approved the products of biotechnology more rapidly than traditional chemical-based pharmaceuticals, but this may be due to the fact that they are generally targeted at life-threatening diseases and therefore receive prompt attention from the FDA. Much of the lengthy development process associated with the biotechnology industry, as well as the significant amounts of capital involved, is due to this regulatory cycle over which the companies have little control.

Historically, the pharmaceutical, diagnostic and food industries were all dominated by very large, multi-national companies able to fund the research and testing needed to bring products to market. In fact, the only company to enter the ranks of major pharmaceutical firms since the Second World War is Syntex, which was founded on breakthroughs in antibiotics. Biotechnology provides a similar opportunity to break into this extremely profitable business. Though the regulatory hurdle may seem daunting for a small company, one of the essential attractions of biotechnology to investors is its potential to overcome the regulations and enter the pharmaceutical marketplace. (Conversely, pharmaceuticals provide a profit incentive large enough to justify the risk involved in developing this new technology.) Genentech demonstrated the correctness of this assessment. In less than 15 years its investors created a pharmaceutical company valued at approximately $3.5 billion by Hoffmann-La Roche.

Local cities and towns have created a very different regulatory environment. A large number of agencies have jurisdiction over the activities of biotechnology companies, and the permitting process can be onerous.

In the early days of Massachusetts biotechnology, the local regulation was a thorny issue, particularly in

Cambridge where much of the early research was conducted. The Cambridge City Council and its mayor Alfred Vellucci drew national headlines by first challenging the safety of recombinant research, and then adopting a regulatory framework that was both the most comprehensive and the most attractive in the United States. Cambridge achieved this by adopting "guidelines" drawn up by the National Institutes of Health as law. These guidelines, though detailed and restrictive, were rational and predictable, and, more importantly, were standard practice in most biology labs. Over the years, the NIH regulations have been revised as scientists have learned more about the technology, but Cambridge is still able to boast the most restrictive regulations in the United States and the largest concentration of biotechnology companies in the world.

The lesson of Cambridge is that the biotechnology industry is not anti-regulation but is willing to accept an extensive regulatory framework as long as it is neither punitive nor unpredictable.

Private vs. Public Financing

A key difference between biotechnology and other commercialized sciences is that biotechnology has received only meager government support. Though the National Institutes of Health has made a major contribution to basic research, the commercialization of biotechnology in the United States has been almost totally privately financed. The Defense Department has traditionally supported emerging technologies by financing their adaptation to military use. The fact that biotechnology is not of major interest to the military has significantly circumscribed the availability of government funds.

Much of the history and character of biotechnology is defined by this lack of government support, by the resulting critical need for private financing, by the laggard response of government agencies to its needs, and by the readiness of foreign investors to fill the void. Clearly, some of this reticence has evolved from the controversies surrounding biotechnology and from a lack of a clear public understanding of its potential value. Whatever initiative has driven this industry forward has come from the individuals involved, and they have depended on notoriety to attract supporters. The net effect has been the creation of a very independent, outspoken,

international industry that has not shied from controversy.

While government funding may have been lacking, the United States investment community has been very supportive of biotechnology. Most new companies traditionally receive their initial funding from venture capital companies. Through much of the 1980's a private pool of over $4 billion was available for investment in early stage ventures. Though much of this was targeted for the computer industry, significant funds were readily available for biotechnology.

Typically, venture capitalists have formed biotechnology companies by spotting technological breakthroughs, seeking the key scientists and offering funding if the scientists are willing to form a company based on their proprietary research. Genentech, the first major biotechnology company, was formed in this manner by Bob Swanson, who at the time was working for Kleiner Perkins, a major West Coast venture capital firm. Massachusetts' Biogen was similarly formed by a group of venture capitalists, including Boston-based TA Associates.

This venture round, as it is called, has traditionally been followed by additional private financings and finally by sale of stock to the public. Since the fall of 1987, however, few biotechnology companies have been able to complete initial public offerings, and only the industry leaders have found the stock market receptive to their needs. This has made it far more difficult for private and venture investors to liquidate their positions and, as time passes, will make them more eager to sell out at less than targeted returns, resulting in mergers, acquisitions or significant foreign investments.

Corporate partners are also an important source of development funding. Generally large pharmaceutical or industrial companies willing to back research or specific products provide both financial support plus big-company expertise. Typically, they support research at a biotechnology company through a partnership, joint venture or equity relationship, thereby reducing their internal risk while gaining the efficiency of a small, entrepreneurial research organization. For example, Merck, the dominant vaccine manufacturer in the

world, supports research toward an AIDS vaccine at Repligen in Cambridge.

The final source of financing is through product sales. The earliest biotechnology companies dismissed the concept of bringing short-term products to the market because they were committed to developing major biopharmaceuticals with vast markets and long development times. However, today a two-tiered strategy of using revenues from early products to support a long-term development strategy has gained popularity. This strategy produces greater stability and preserves future profits for the company and its stockholders. The most successful follower of this strategy has been Genzyme, based in Cambridge, and its success has increased the number of companies adopting this model.

Not All Biotechnology Companies Are Start-Ups

The hope of those in the biotechnology industry in Massachusetts has always been that a local company would become a major pharmaceutical firm. The Commonwealth now has three clear candidates: Biogen, Genetics Institute and Genzyme, all located in Cambridge. We are also seeing new potential for regional growth in the decision of major pharmaceutical firms to participate directly in the Massachusetts biotechnology community. For example, Serono Laboratories, the American subsidiary of a Swiss pharmaceutical company, currently employs over 200 people in its Massachusetts facility and has recently built a state-of-the-art research and production facility that will employ another 130 people by year end. BASF, the large German chemical company, is building a major biopharmaceutical research facility in Worcester that will eventually employ over 500 people.

Two Japanese firms, Nissen and Eisai Pharmaceuticals, have already established biotechnology research outposts in Andover and Cambridge. Others are rumored to be considering the establishment of similar facilities. A significant additional lure for such companies is the major regional real estate projects currently in the planning stage. Though real estate development must stay ahead of trends and not every project on paper gets built, projects such as the Tufts development in the South Station area or the Charlestown Navy Yard

expansion will create significant space availability, and local real estate firms will launch international promotional campaigns to seek tenants.

Geographic Distribution

Two concentrations of biotechnology companies deserve special attention: Cambridge and Worcester. There is no other place in the biotechnology universe like Cambridge. It is both the center of the science and the center of the industry. MIT has long dominated the study of life on a molecular level, and Harvard runs a close second. It is therefore no surprise that numerous companies have been founded in the shadow of these two universities. In addition to proximity to such research institutions, the controversy over regulations in the early 1980's put in place regulatory structures early, so that the city leaders could say that Cambridge had the most stringent regulations of any city in the world (which is probably still true), while the companies had assurance that these rules were set and would not change precipitously.

While the industry was establishing its center in Cambridge, Worcester foresaw the opportunity to become a major satellite. In 1984, the Massachusetts Centers of Excellence Corporation helped support Worcester's efforts to become a site for development of the biotechnology industry. Immediately prior to that, the city established a set of regulations and ground was subsequently broken for the Massachusetts Biotechnology Research Park in Worcester. In that year, the Massachusetts Biotechnology Research Institute, a consortium of universities and research institutes, began receiving direct support from the Massachusetts Centers of Excellence Corporation. The support constituted shared equipment and technology transfer activities, including an incubator for the formation of new businesses in the park.

Today, in addition to having two major biotechnology companies located there (Transgenic Sciences and Cambridge Biotech Corp.), Worcester serves as an incubator for a number of new companies established through Commonwealth BioVentures and others and will house the BASF biotechnology research center (currently under construction). When this construction phase is completed, the Massachusetts Biotech Research Park in Worcester

will contain over 615,000 square feet of rentable space, of which 96 percent is currently under agreement.

Geographic Distribution

Cambridge	33
Boston	7
Worcester	5
Newton	6
Woburn	4
Lexington	4
Needham	3
Hopkinton	3
Bedford	3
Billerica	2
Framingham	3
Malden	3
Watertown	3
Other	37
Total:	116

THE SURVEY DATA

The survey questionnaire was designed to be completed and returned by a single individual within a company, so it requested estimates rather than precise numbers and sought financial data in the form of ranges so that companies not normally required to disclose such information would be encouraged to do so. The respondents were all promised anonymity, and therefore no individual company data is provided in this report.

Survey Response

Number of Companies in MA	116
Number of Respondents	66
Response Rate	57%

A total of 66 companies completed the survey, 57 percent of the defined universe. We then proceeded to contact the remaining companies to gain basic information, such as number of employees and founding date for use in extrapolating the data. This data was successfully collected from a total of 91 companies or 78% percent of the total.

The industry has been divided into four groups: therapeutics, diagnostics, agriculture and other. Therapeutic companies are devoted to the development of medicines for human use; diagnostic companies develop products used to detect or evaluate disease; agriculture is involved with farms, plants or animals, and other includes the manufacturers of biotechnology supplies or implements.

Interpreting the Data

No aspect of biotechnology is more controversial in Massachusetts than estimates of its eventual contribution to the economy. Forecasting is always problematic, but accurate forecasts of an industry still in the early stages of its development and built on expectations is particularly difficult. Clearly, not every company will meet its goals or even survive the decade. Failure is an integral part of our economic system, yet very few biotechnology companies have failed to date. Expectations for young companies are far more subjective than those for more mature businesses with a well established planning process. Changes in the general business climate or research advances may have a significant effect on biotechnology. Entrepreneurs by their nature must be optimists, and their estimates of growth will reflect this positive sensibility.

Survey Computation

Over 55% of the companies polled responded with completed questionnaires. We were therefore able to extrapolate reasonable industry data based on the returned estimates For example, we were able to get employee data for almost 80% of the companies. To estimate total employees, we averaged the employee base and multiplied it out over the total number of companies. Therefore, the results should be regarded as ranges and not as definitive.

We asked companies, particularly in the area of employees, to estimate what they thought their employee needs would be in three years and in ten years. We then took that data and derived average percentages of growth. This growth estimate does not indicate how many people will be employed in Massachusetts, but how many people will be employed by these companies if they attain their goals. In even the best case, a certain percentage of these employees will be employed elsewhere.

Projections of potential employment are both highly speculative and highly subjective. Therefore we are offering no absolute number for estimated employees either in the next two years or the next ten. Clearly, biotechnology is not an employee intensive business like the computer industry but it

does have the potential of making a significant economic contribution to the Commonwealth.

Industry Profile

A composite can be drawn of the average biotechnology company in Massachusetts. It has 121 employees and an estimated payroll of $3.7 million. It is located in Cambridge and was founded in either 1980 or 1985 and spends approximately $11 million in Massachusetts each year. It expects to have a 57 percent increase in total staffing by 1993 and a 388 percent increase in employment by the end of the decade.

Of the three primary areas of activity the therapeutics sector of the biotechnology industry which is developing medicines for human use is currently the largest and is projecting the greatest growth. Therapeutics companies constitute the largest single group surveyed (41 percent) and represent what most people think of when they envision a biotechnology company. They are also the companies with the longest R&D cycle. Therefore, the industry leaders - those companies founded in the late 1970's - are just now getting products on the market after a decade of development. All forecast exponential growth as new products come to market. Recent history confirms these expectations. Early biotechnology products such as alpha interferon, tissue plasminogen activator, human insulin and human growth hormone and erythropoietin are each individually generating hundreds of millions of dollars in annual revenues.

Average Company Profile

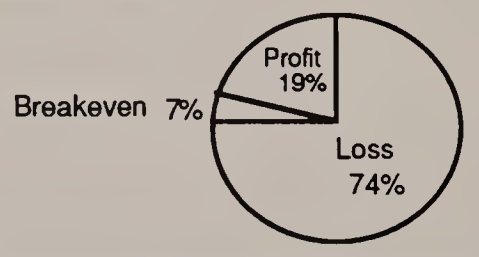
Number of Employees/Company	121	
Employees by Area		
Research and Development	44%	
Administration and Marketing	31%	
Manufacturing	24%	
Projected Increases in Staffing	In 3 Years	In 10 Years
Research and Development	44%	194%
Administration and Marketing	35%	285%
Manufacturing	93%	686%
Expenses in Massachusetts	$11.4M	
Annual Profile	$3.7M	
Cash Reserves	$12.1M	

Therapeutics companies also tend to be somewhat larger than other biotechnology companies with an average of 133 employees and a $4.0 million payroll, though this number is somewhat skewed by the presence of four companies with employees numbering significantly over 300. As expected, over 74 percent of the companies reported losses, and only 19 percent said they were profitable. A third of the therapeutics companies reported revenues over $10 million and 43 percent reported expenses in excess of that amount.

Therapeutics Company Profile

Average Number of Employees	133
Average Annual Payroll	$3.97M
Average Products in R&D	7

Companies Operating at a

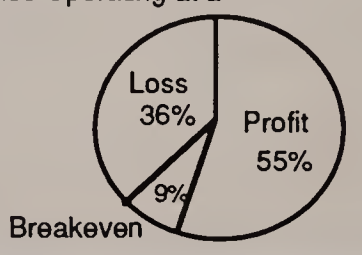


Diagnostic products have a much shorter development cycle than therapeutics and are therefore a more mature industry. Diagnostic companies forecast a growth rate of about half of the therapeutic companies over the decade, but expect about twice the therapeutic company growth rate over the next three years.

Diagnostic Company Profile

Average Number of Employees	98
Average Annual Payroll	$3.6M
Average Products in R&D	7

Companies Operating at a



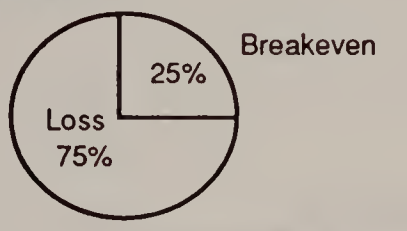
Diagnostic companies averaged 98 employees with a payroll of $3.6 million. Over half reported

profitability, reflecting the shorter product development cycle. Diagnostic companies tend to be smaller than therapeutic companies, and the 98 employees per company figure may be skewed by a few very large companies located in the state, as is reflected by the 64 percent that reported revenues of under $5 million, with only 27 percent reporting revenues over $10 million. Similarly, 68 percent reported expenses under $5 million, 25 percent over $10 million and eight percent over $20 million.

Agricultural Company Profile

Average Number of Employees	48
Average Annual Payroll	$1.4M
Average Products in R&D	22

Companies Operating at a



Biotechnology companies working in agriculture constitute the smallest segment of the industry and are the least well developed. The fact that they are here at all is proof of the power of the Massachusetts research community. Most of the agricultural companies are small, with four of the five companies reporting fewer than 50 employees and a total payroll averaging $1.36 million per company. The largest of these, BioTechnica International with 315 employees worldwide, is a developer of improved seed lines through genetic engineering. Another is Newton-based Safer with 30 employees, which manufactures and markets non-toxic, biodegradable pesticides. None are currently profitable, and one reported break-even. Four of the five reporting companies were under $5 million in both revenues and expenses, with one company in the $10 to $20 million range for revenues and expenses.

Area for Potential Growth

The greatest area for potential employment growth lies in the manufacturing sector of the industry. Proximity of manufacturing to management and R&D is not crucial, and many mature pharmaceutical companies have manufacturing facilities located at some distance from corporate offices. This is also true with agricultural companies whose markets are often far from the research centers. Therefore, even at best it would be unreasonable to expect Massachusetts to capture all of the potential growth in manufacturing employment (projected at 93 percent in three years and 686 percent in ten.) The challenge for the Commonwealth will be to hold on to as much manufacturing as possible, to attempt to attract additional manufacturing to the state from companies based elsewhere, and to prevent manufacturing out-of-state to become the industry norm.

Siting Criteria

Just over 84 percent of the companies reported that proximity to a university was important and 35 percent listed it as their first priority in site selection. It is therefore no surprise that 33 (35 percent) of the biotechnology companies surveyed are located in Cambridge, with nine in Boston, primarily near the teaching hospitals.

When the respondents were asked to rank their criteria for selecting a location, cost was also a clear consideration. 41 percent of the companies stated that cost was their first siting criteria and 24 percent said it was their second. We therefore find companies scattered throughout the eastern sector of the state, with major concentrations in the Needham/Newton area, along Route 128 and in Worcester.

Biotechnology companies report a clear preference for being close to research institutions. However, competition for siting is intense and 74 percent of the companies responding noted that they had been contacted by other states about relocating or locating expanded facilities. Three states -- New Hampshire, California and Rhode Island -- were cited as most aggressive in recruiting and as most attractive to management.

Siting Criteria

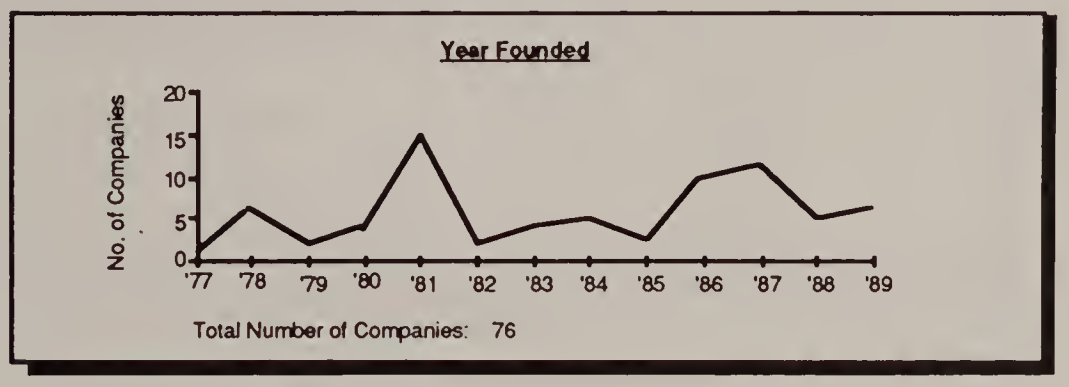
Ranking	First	Second
Proximity to Research Center	35%	21%
Cost	41%	24%
Employee Convenience	15%	24%

General Importance	
Proximity to University Important	85%
Proximity to Hospital Important	58%

Companies Planning New Sites	44%
New Site Planned for Mass.	41%

New Companies Started

Two three-year periods saw the most active founding of new biotechnology companies: 1980-82 and 1986-88. Out of 91 companies suppling data on when they were founded, 22 (24 percent) were founded in the first period, and 26 (29 percent) were founded in the latter period.



Biggest Challenges

Financial worries lead the industry list of near-term concerns. This is no surprise since the industry that has yet to achieve broad profitability or mature products. Historically, biotechnology companies are far more affected by swings on Wall Street than by product markets. The effects of the market crash of October 1987 are still felt. There have been few periods in which public offerings could be completed with ease, and initial public offerings continue to be rarities.

What Is Your Biggest Challenge in the Next Three Years?

Financing	58%
Personnel	38%
Regulatory	35%

Recruiting is also a major concern for biotechnology companies, reflected by the 38 percent of respondents who listed this as their biggest challenge over the next three years. The issue is not one of attracting employees to the industry, for indeed newness is significantly attractive in itself, but of finding qualified employees. As noted elsewhere in this report, the industry pays well on average and young companies always have the additional enticement of stock participation.

As biotechnology has grown, companies have experienced intense competition for employees who possess the correct mix of an understanding of standard business practices in more mature industries (primarily pharmaceutical) and an entrepreneurial spirit. From the CEO on down through the ranks of management, it has been difficult to find those individuals who have had relevant prior experience. As the companies expand into manufacturing, the problem continues to grow as the need for highly specialized technicians increases. During early entrepreneurial stages, senior management and researchers often wear many hats. As companies grow, a limiting factor on the rate of growth is the necessity of finding the right people to wear each of those hats.

One of the reasons why biotechnology companies tend to cluster is the availability of employees. Massachusetts has been active in the training of employees for the industry, particularly through the aegis of the Bay State Skills Corp. and innovative programs both at local community colleges and four-year institutions. This has constituted one of the

Commonwealth's major advantages in attracting both start-ups and mature research centers.

Is the Massachusetts Regulatory Environment?

Excellent	3%
Good	27%
Fair	49%
Burdensome	21%

Were Local Regulations an Issue in Site Selection?

No	40%
Major Factor	35%
Minor Factor	25%

Have You Experienced Local Regulatory Difficulties?

No	39%
Minor	32%
Annoying but not severe	29%
Severe	0%

Do You Find Local Authorities:

Accommodating	52%
Uninterested	42%
Hostile	6%

What Do You Think the Regulatory Environment is Versus

	Other states	California
Better	12%	2%
Good	28%	10%
Same	35%	58%
Worse	25%	30%

The regulations that most biotechnology companies fear come from the federal agencies that rule on the safety and effectiveness of new products. Few of these agencies have had the funding required to keep pace with a dynamic, expanding industry. Their ability to persevere has been due primarily to the willingness of agency employees to work long hours for low pay to compensate for underfunding and under-staffing.

The weakening of the regulatory system has increased the unpredictability of the process, particularly regarding how long a review takes to be completed. Though there is little that state agencies can do to correct problems in the federal regulatory system, industry watchers must be increasingly sensitive to the problems of predicting regulatory approval, a key component in forecasting the time a product will reach the market. Companies have

become increasingly hesitant to predict the time involved in the regulatory process. While a year or two lost in additional clinical testing or delayed agricultural field trials may not appear important in the full scheme of product development, it can seem like forever if it coincides with a cycle of investor skittishness or public demands to know "what biotechnology has done for me lately."

On a local level, regulatory issues are a major concern in site selection for a third of the respondents, a minor issue for a third and not an issue for the remaining third. When asked how many had experienced local regulatory difficulties, no one reported severe difficulties, and approximately a third each reported no difficulties, minor difficulties or annoying but not severe difficulties. Over 90 percent of the companies responding reported local authorities (the essence of almost all regulatory issues) either accommodating or neutral. Ten years of experience have obviously had their effect in lessons learned and confidence built. A decade of virtually trouble free operation has reduced the adversarial supervision of biotechnology of the early 1980's to a collaborative effort to assure public safety.

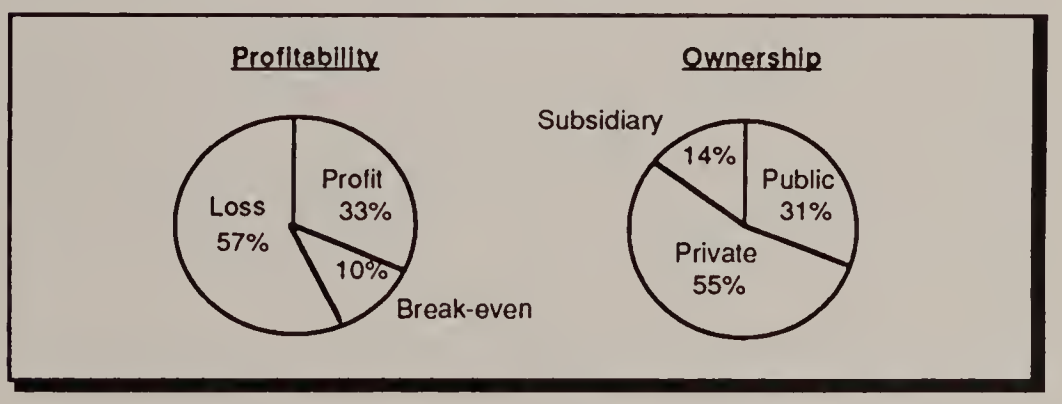
The resolution of the regulatory issue is a major selling point for the Commonwealth. Biotechnology companies do not seek a regulation-free environment. They prefer predictability and freedom from harassment. This is best achieved by having a strong set of regulations in place that build public confidence in the oversight process and provide a framework for growth and technical change. Cambridge in particular provides an attractive environment for biotechnology, having put in place comprehensive regulations a decade ago which have operated smoothly since. These regulations, hailed as the most stringent in the world, ended the period of public debate and began the expansion of biotechnology in Cambridge.

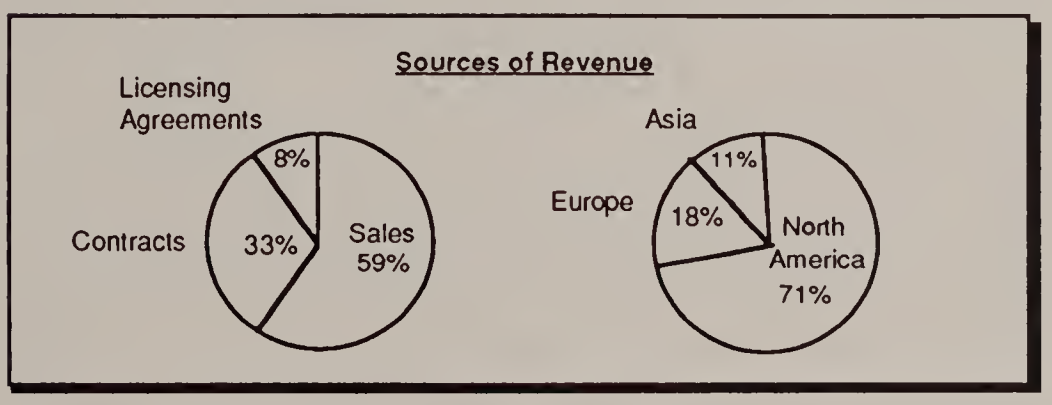
Financial Profile

The survey provided confirmation of several aspects of the industry generally regarded as common knowledge: most of the companies are currently showing losses or are at a break-even point; a significant portion of revenues are from research contracts and industry sales; and R&D accounts for almost half of expenses industry-wide.

Though biotechnology companies tend to go public relatively early in their development, only 31 percent of the Massachusetts biotechnology industry is composed of public companies. The remainder are either private concerns (55 percent) or are subsidiaries (14 percent) of other companies.

Collecting financial data is difficult because only public companies are required to disclose such information. We therefore asked respondents to give us estimated revenues within a set range. Using this technique, the total annual revenues for the responding companies were in the range of $794 million and $1.3 billion. The annual expenses were between $782 million and $1.4 billion.





We also asked companies for the total amount of money they spent in Massachusetts and the total size of their payroll. For the former, the industry total was

$432 million for an average of $3.72 million per company. Using these figures, a total average payroll of approximately $30,700 per employee was derived.

Respondents were asked to estimate their total cash reserves, a critical figure for companies in an R&D phase. The 43 companies responding to this question had a total cash reserve of $518 million or an average of $12.04 million per company reporting.

Most of the companies showing profits sell either diagnostic products or manufacture equipment and supplies for use by biotechnology companies. However, a successful pharmaceutical product can produce income in the hundreds of millions of dollars and can have market exclusivity for over 17 years if patented. Only one therapeutic product developed by a Massachusetts company, alpha interferon, is currently on the market in the U.S., producing sales for the licensee (Schering Corp. located in New Jersey) of over $150 million a year and producing a royalty flow back to Biogen generally believed to be about 10 percent of sales. Serono Laboratories, the American subsidiary of a Geneva-based pharmaceutical firm with significant manufacturing, marketing and research facilities in the Boston area, currently manufactures genetically engineered human growth hormone in Randolph, MA, which is exported for sale abroad and fertility hormones for use in treating sterile women.

THE FUTURE

Economic Contribution

Though biotechnology is not a labor-intensive business, it can be expected to make a significant contribution to the economy of Massachusetts, both through the employment of tens of thousands of people and through the infusion of hundreds of millions of dollars of expenditures into the local economy. The primary need over the next decade will be for qualified labor in manufacturing plants which report a projected growth of 815 percent. However, making the products of biotechnology is not as labor intensive as traditional manufacturing businesses and it is unlikely that it will ever be a dominant contributor to the employment pool such as the computer industry has been over the past two decades.

Indirect employment, jobs in the industries and service businesses that support biotechnology, is likely to be higher than for traditional manufacturing. For example, biotechnology facilities are complex and require extensive plumbing, electrical and ventilation facilities. The biotechnology manufacturing process makes heavy reliance of computers and advanced equipment, and biotechnology has reached the point where local legal firms have established biotechnology practices. Like any business with a common set of needs, biotechnology has established and will continue to rely upon a support structure that will have a reputation equal to the industry. All of this expertise can be marketed to companies outside of Massachusetts and bring income into the state, so long as the biotechnology industry remains strong here.

Salaries at biotechnology companies are relatively high, averaging $31,700 per employee, so that the average employee also makes a larger-than-average contribution to the local economy both in the form of taxes and personal expenditures. Though

the salary average can be expected to decline somewhat as the ratio of senior management to total employees drops, the industry can be expected to continue to be relatively high paying over the decade.

Continued Growth

Though Massachusetts's pre-eminence in R&D has given it a lead in the developing biotechnology industry, there can be no guarantee that the continued growth of these companies will occur here. Manufacturing, which has the greatest potential for employment, does not have to be located close to senior management or R&D. There is however no reason to conclude that manufacturing will not locate in the Commonwealth, only that there will be intense competition from other areas of the country. In addition, Massachusetts has the potential of attracting the R&D arms of major pharmaceutical companies to the state. This also is likely to be a very competitive arena.

Based on the survey, senior biotechnology executives continue to expect significant growth through the 1990's as their products reach the market. However, a number of variables outside the industry will directly affect the rate of growth. Particularly important is the strength of the financial markets which will continue to provide the wherewithal for growth before the industry can become product driven. Another significant variable is the continuing rate of scientific discovery. Though we have just begun to understand the dynamics of the technology and it will take some years to fully commercialize what we already know, much of the vitality of Massachusetts's biotechnology sector comes from start-up companies which are dependent on new ideas.

Foreign competition is likely to become intense as the industry matures. Some of these companies, such as Serono and BASF, will find it convenient to establish outposts in the Boston area. Others, such as the large Japanese and European pharmaceutical firms that have made significant investments in the products of U.S. biotechnology companies, are liable to bring the future of these products into their own corporate structure, thereby curtailing the growth potential of their entrepreneurial partners. The availability of private financing,

currently a significant unknown, will be critical to the continued growth of the biotechnology industry. If consolidation becomes the only means of fueling product development, the total number of companies may shrink and the founding of new companies may slow.